IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: '318 PATENT INFRINGEMENT LITIGATION	)	Civil Action No. 05-356-KAJ (consolidated)
	)	**REDACTED PUBLIC VERSION**

PLAINTIFFS' MEMORANDUM IN SUPPORT OF MOTION FOR PARTIAL SUMMARY JUDGMENT REGARDING ANTICIPATION UNDER 35 U.S.C. § 102

Of Counsel

George F. Pappas
Roderick R. McKelvie
Christopher N. Sipes
Kurt G. Calia
COVINGTON & BURLING
1201 Pennsylvania Avenue, N.W.
Washington, DC 20004
202-662-6000

Steven P. Berman
Office of General Counsel
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933
732-524-2805

ASHBY & GEDDES
Steven J. Balick (I.D. #2114)
John G. Day (I.D. #2403)
Tiffany Geyer Lydon (I.D. #3950)
222 Delaware Avenue, 17th Floor
P.O. Box 1150
Wilmington, DE 19899
302-654-1888
sbalick@ashby-geddes.com
jday@ashby-geddes.com
tlydon@ashby-geddes.com

Attorneys for Plaintiffs

Dated: November 17, 2006

TABLE OF CONTENTS

TABLE OF AUTHORITIES

STATUTES

INTRODUCTION

Defendants Alphapharm Pty Ltd. ("Alphapharm") and Barr Laboratories, Inc. and Barr Pharmaceuticals, Inc. (collectively, "Defendants") have challenged the validity of U.S. Patent No. 4,663,318 ("the '318 Patent") alleging that Claims 1 and 4 are invalid. (The '318 Patent is attached as Exhibit A.) The '318 Patent claims a method of using galantamine hydrobromide, marketed by Plaintiffs under the trademark RAZADYNE®, in the treatment of Alzheimer's disease.[1] After Defendants filed Abbreviated New Drug Applications ("ANDAs") with the U.S. Food and Drug Administration ("FDA") to market generic versions of RAZADYNE, which included certifications that the '318 Patent is invalid, Plaintiffs, Janssen Pharmaceutica, N.V., Janssen L.P, and Synaptech, Inc. (collectively, "Plaintiffs"), brought this suit. Defendants concede that the sale of the drug products described in their ANDAs would infringe Claims 1 and 4 (*see* 12/2/05 Stipulation Not to Contest Infringement (D.I. 49)), and the only remaining issues relate to Defendants' invalidity defenses. Defendants' anticipation defense is based solely on a 1974 reference titled "Medical Management of Dementia," attached as Exhibit B ("Bhasker").[2]

A claimed invention is anticipated by a prior art disclosure only if "[t]here must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *Forest Labs., Inc. v. Ivax Pharms, Inc.*, 438 F. Supp. 2d 479, 485 (D. Del. 2006) (quoting *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991)). Also, a party alleging anticipation must

---

1 RAZADYNE® is a registered trademark. However, for purposes of this motion, Plaintiffs will refer to the RAZADYNE product without using the trademark symbol.

2 P.A. Bhasker, "Medical Management of Dementia," *The Antiseptic*, 71:45-47 (1974).

show that a single reference discloses each of the claim elements in the asserted claim. *See, e.g., Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002); *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) ("Invalidity by anticipation requires that the four corners of a single, prior art document describe every element of the claimed invention...."). Bhasker does not disclose any of the elements of Claims 1 and 4 of the '318 Patent.

Accordingly, Plaintiffs are entitled to partial summary judgment dismissing Defendants' anticipation defenses and related counterclaims.

STATEMENT OF FACTS

A. The '318 Patent and RAZADYNE

The '318 Patent was issued by the United States Patent and Trademark Office ("PTO") on May 5, 1987 to its inventor, Dr. Bonnie M. Davis, and it expires on December 14, 2008. It was exclusively licensed to Janssen Pharmaceutica N.V. on November 30, 1995. Claim 1 of the '318 Patent[3] describes the invention of treating Alzheimer's disease using galantamine and reads as follows:

> A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

Ex. A '318 Patent, 3: 6-10.

Janssen holds an approved new drug application ("NDA") for galantamine hydrobromide tablets used in the treatment of mild to moderate Alzheimer's disease and currently markets the tablets under the name "RAZADYNE" (formerly called "REMINYL").

---

[3] Claim 4 is directed to a method relating to Claim 1 and specifying a dosage range for oral administration, but for purposes of this motion, need not be considered separately.

B. The Bhasker Article

Defendants rely solely on Bhasker to support their anticipation defense. Bhasker, a roughly two-page review of treatment approaches for certain forms of dementia, never mentions Alzheimer's disease at all, let alone any treatment for that disease. Moreover, Bhasker emphasizes the importance of promptly determining whether a demented patient is suffering from a treatable or untreatable dementia, and describes "progressive dementias" – which defendants contend would refer to Alzheimer's disease[4] – as untreatable: "With regard to progressive dementia, there appears very little to offer. Only management and no treatment is possible." Ex. B *Bhasker* at 45.

Bhasker's only reference to galantamine is in reporting Dr. Alexander Luria's work in treating "local brain damage," a condition that is entirely different from Alzheimer's disease. Specifically, Bhasker states:

> The restoration of higher cortical functions is difficult and was once considered …impossible; but it has lately gained importance. Luria and his colleagues have dealt with this problem in great detail. They have suggested measures of improving the higher functions in cases of local brain damage like tumour, head injury, infarct etc, by deinhibitory procedures and re-education of the rest of the brain. Deinhibition refers to the facilitation of acetylcholine activity by giving small daily doses of Cholinesterase inhibitors (Neostigmine, Gallanthamine etc.). Ex. B *Bhasker* at 46.

It is undisputed that Alzheimer's disease is not a form of local brain damage and that Luria did not study or treat Alzheimer's disease (and Defendants do not cite any Luria publication as anticipating the '318 Patent).

---

[4] *See* Defendant Alphapharm Pty., Ltd.'s First Supplemental Response to Interrogatory No. 2 of Plaintiffs' First Set of Interrogatories (Ex. C) at pp. 4-5; Defendants Barr Pharmaceuticals, Inc.'s and Barr Laboratories, Inc.'s Supplemental Objections and Response to Plaintiffs' Interrogatory No. 2 (Ex. D) at 4-5.

Far from disclosing each of the elements of the '318 Patent Claim 1, Bhasker does not teach or suggest anything about Alzheimer's disease treatment at all (let alone treatment with galantamine) except to the extent it states that progressive dementias are untreatable.

ARGUMENT

A. Standard for Summary Judgment

Summary judgment serves the important function of eliminating factually unsupported claims and defenses, thereby avoiding unnecessary trials. *See Celotex Corp. v. Catrett*, 477 U.S. 317, 323-24 (1986). Consistent with this purpose when confronted with a properly supported motion for summary judgment on issues as to which it bears the burden of proof at trial, a party must respond with evidence sufficient to establish the essential elements of its case. *Id.* at 322-23. In addition, "[w]hen the moving party has carried its burden under Rule 56(c), its opponent must do more then simply show that there is some metaphysical doubt as to the material facts." *Matsushita Elec. Indus. Co., Ltd. v. Zenith Radio Corp.*, 475 U.S. 574, 586 (1986) (footnote omitted). Importantly, "in ruling on [the instant] motion for summary judgment, the [Court] must view the evidence presented through the prism of the substantive evidentiary burden." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 254 (1986); *see also Quad Envtl. Techs. Corp. v. Union Sanitary Dist.*, 946 F.2d 870, 872 (Fed. Cir. 1991).

In this case, the burden of proof facing Defendants is formidable. Defendants must first overcome the strong statutory presumption that the '318 Patent is valid. 35 U.S.C. § 282. Decision making begins by accepting the proposition that the patent is valid and then looking to the challenger for evidence to the contrary. *Lear Siegler, Inc. v. Aeroquip Corp.*, 733 F.2d 881, 885 (Fed. Cir. 1984). Accordingly, Defendants must prove anticipation by clear and convincing evidence. *See Schumer v. Lab. Computer Sys., Inc.*, 308 F.3d 1304, 1315 (Fed. Cir. 2002); *Union Carbide Chems. & Plastics Tech. Corp. v. Shell Oil Co.*, 308 F.3d 1167, 1188

(Fed. Cir. 2002); *Helifix Ltd. v. Blok-Lok Ltd.*, 208 F.3d 1339, 1345-46 (Fed. Cir. 2000). To avoid summary judgment, Defendants must show there are material disputed issues of fact that could clearly and convincingly establish anticipation.

B. Standard for Anticipation

"Anticipation under [35 U.S.C.] § 102(a) requires that the identical invention that is claimed was previously known to others and thus is not new." *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1267 (Fed. Cir. 1991).

Thus, anticipation occurs when a single prior article, patent, or publication contains within its four corners every element of the claimed invention. *Advanced Display Sys.*, 212 F.3d at 1282. An individual reference cannot anticipate if it does not clearly disclose each and every element of each asserted claim, *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1473 (Fed. Cir. 1997). *See also Impax Labs. v. Aventis Pharms., Inc.*, 235 F. Supp.2d 390, 392 (D. Del. 2001) ("anticipation under section 102 requires that each and every limitation of the claimed invention be disclosed in a single prior art reference," quoting *In re Paulsen*, 30 F.3d 1475, 1478-79 (Fed. Cir. 1994) (citing *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990)).

C. Bhasker Does Not Anticipate The Claims Of The '318 Patent Because It Does Not Disclose "Each And Every Limitation Of The Claimed Invention," Including The Use Of Galantamine To Treat Alzheimer's Disease

The only mention of galantamine in Bhasker is a passing reference to the work of a Soviet neuropsychologist, Dr. Alexander Luria, in connection with the treatment of "local brain injury" – a very different condition from Alzheimer's disease. Bhasker identifies "Neostigmine, Gallanthamine etc." as examples of cholinesterase inhibitors that had been suggested by Dr. Luria as possible treatment "in cases of local brain damage like tumour, head injury, infarct etc." The two compounds mentioned are not described as a treatment for Alzheimer's disease or, for that matter, any progressive dementia. To the contrary, as noted, Bhasker states that "[w]ith

regard to progressive dementia, there appears very little to offer. Only management and no treatment is possible." Ex. B *Bhasker* p. 45.

In this regard, this Court's decision in *Impax*, 235 F. Supp.2d at 395, is closely on point. There, Impax contended that the claimed invention of the '814 patent was anticipated by a paper written by Edith McGreer that discloses that riluzole can protect against the neuronal degeneration associated with Amyotrophic Lateral Sclerosis ("ALS") by inhibiting EAA release. In response, Aventis contended, supported by its expert, that the McGreer paper did not state that riluzole treats ALS, and that the McGreer paper refers to riluzole in only one diagram with no elaboration or discussion, without disclosing each element of the claimed invention of the '814 patent. This Court, accordingly, concluded that the McGreer article does not teach the use of riluzole to treat ALS. *Id.* at 395; *see also Forest Labs.*, 438 F. Supp. 2d at 486 (reference disclosing the individual enantiomers of a compound does not anticipate a claim to a substantially pure enantiomer where the reference does not say anything about purity).

Here, the Defendants anticipation claim is, if anything, even more defective than that in *Impax* or *Forest Labs*. While those cases rejected anticipation on the basis of the absence of any express teaching in the reference, Bhasker's express teachings *contradict* defendants' anticipation claim. It is simply beyond the pale of reasonable dispute to contend, as defendants must, that an article describing progressive dementia as untreatable instead describes a treatment for the progressive dementia of Alzheimer's disease, or that a description of galantamine in connection with "local brain damage" instead describes its use for that wholly different disease. As a matter of law, Defendants cannot meet their burden to prove anticipation by clear and convincing evidence with such a twisted and contrary reading of Bhasker. *See Motorola*, 121 F.3d at 1473; *Impax* at 392.

The failure of Bhasker to anticipate the '318 Patent is confirmed by the November 13, 2006, deposition testimony of Defendants' own expert, Dr. Edward Domino.

REDACTED

The settled law of anticipation forbids this sort of argument. As this Court emphasized recently in *Forest Labs.*, to anticipate a reference must teach "the entirety of the invention.... [O]ne skilled in the art cannot supply missing elements through his or her knowledge." 438 F. Supp. 2d at 485; *see also Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984) (citing *In re Foster*, 343 F.2d 980, (C.C.P.A. 1965), and rejecting the argument that "missing elements may be supplied by the knowledge of one skilled in the art or the disclosure of another reference"); *Rockwell Int'l Corp. v. SDL, Inc.*, 103 F. Supp. 2d 1202, 1206 (N.D. Cal. 2000) (same). Because Bhasker indisputably does not itself describe

Alzheimer's disease, let alone galantamine's use as a treatment for that condition, Defendants' anticipation claim fails as a matter of law.

CONCLUSION

For the foregoing reasons, this Court should grant Plaintiffs' motion for partial summary judgment and dismiss Defendants' defenses and related counterclaims based on anticipation under 35 U.S.C. Section 102.

ASHBY & GEDDES

/s/ Tiffany Geyer Lydon

Steven J. Balick (I.D. #2114)
John G. Day (I.D. #2403)
Tiffany Geyer Lydon (I.D. #3950)
222 Delaware Avenue, 17th Floor
P.O. Box 1150
Wilmington, DE 19899
302-654-1888
sbalick@ashby-geddes.com
jday@ashby-geddes.com
tyldon@ashby-geddes.com

Attorneys for Plaintiffs

Of Counsel

George F. Pappas
Roderick R. McKelvie
Christopher N. Sipes
Kurt G. Calia
COVINGTON & BURLING
1201 Pennsylvania Avenue, N.W.
Washington, DC 20004
202-662-6000

Steven P. Berman
Office of General Counsel
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933
732-524-2805

Dated: November 17, 2006
175304.1

EXHIBIT A

United States Patent [19]
Davis

[11] **Patent Number: 4,663,318**
[45] **Date of Patent: May 5, 1987**

[54] **METHOD OF TREATING ALZHEIMER'S DISEASE**

[76] Inventor: **Bonnie Davis**, 17 Seacrest Dr., Huntington, N.Y. 11743

[21] Appl. No.: **819,141**

[22] Filed: **Jan. 15, 1986**

[51] Int. Cl.[4] **A61K 31/55**
[52] U.S. Cl. **514/215**
[58] Field of Search 514/215

[56] **References Cited**

PUBLICATIONS

Chem. Abst. (81)–72615z (1974).
Chem. Abst. (86)–115157z (1977).
Horshenson et al. J. Med. Chem. vol. 29, No. 7, 7/86, pp. 1125–1130.
Kendall et al., J. Chem. & Hospital Pharmacol., (1985) 10–327–330.
S. Chaplygina et al., J. of Highest Nervous Activity vol. XXIV 1976 Issue 5, pp. 1–4.
Krause, J. of Highest Nervous Activity, vol. XXII, 1974, Issue 4.

Primary Examiner—Stanley J. Friedman
Attorney, Agent, or Firm—Ladas & Parry

[57] **ABSTRACT**

Alzheimer's disease may be treated with galanthamine.

7 Claims, No Drawings

METHOD OF TREATING ALZHEIMER'S DISEASE

GENERAL FIELD OF THE INVENTION

The present invention relates to a novel method of treating Alzheimer's disease and more particularly to a treatment using galanthamine.

BACKGROUND ART

Galanthamine and acid addition salts thereof have, for many years, been known to have anticholinesterase properties. Cozanitis in Anaesthesia 29 163–8 (1974) describes the effect of galanthamine hydrobromide on plasma cortisol of patients receiving relaxant anaesthesia and Cozanitis et al in Acta Anesth. Scand. 24:166–168 (1980) describe the effect of galanthamine on plasma ACTH values during anaethesia. These studies showed an increase in both plasma cortisol and plasma ACTH when galanthamine was administered to patients together with atropine.

Il'yuchenok et al (Chemical Abstracts 70 36296K describe the appearance of θ-rhythm on an electroencephalogram when galanthamine is administered intravenously to rabbits.

Increase in short-term memory in dogs by use of galanthamine is described by Krauz in Chemical Abstracts 81 72615Z.

The antagonistic effect of galanthamine to scopolamine-induced amnesia in rats is described by Chaplygina et al in Chemical Abstracts 86 115157Z, and in Zhurnal Vysshei Nervnoi Deiatelnosti imeni P. Pavlova (MOSKVA) 26:1091-1093, 1976.

Alzheimer's disease, presenile dementia, causes much distress not only to those suffering from the disease, but also those who are close to them. The custodial care of advanced victims of the disease is a tremendous expense to society. At present, there is no effective means of improving the functional status of persons with the disease.

It is an object of the present invention to improve the cognitive function of patients with Alzheimer's disease.

SUMMARY OF THE INVENTION

A method for treating Alzheimer's disease and related dementias which comprises administering to mammals, including humans, an effective Alzheimer's disease cognitively-enhancing amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof. A radioactively-labelled form of the molecule may also serve as a diagnostic test for Alzheimer's disease.

DETAILED DESCRIPTION OF THE INVENTION

Galanthamine can be administered in any convenient chemical or physcial form. For example, it may be administered as its hydrobromide, hydrochloride, methylsulfate or methiodide.

Galanthamine or its pharmaceutically-acceptable acid addition salts may be administered to a patient suffering from Alzheimer's disease orally or by subcutaneous or intravenous, injection, or intracerebroventricularly by means of an implanted reservoir. It may be necessary to begin at lower doses than are ultimately effective.

Galanthamine and its acid addition salts form crystals. They are in general only sparingly soluble in water at room temperature and so injectible compositions are normally in the form of an aqueous suspension. If necessary, pharmaceutically-acceptable suspension aids may be employed. Typically, such a suspension will be employed at a concentration of 1–50 mg/ml more commonly 5–40 mg/ml, for example, 5–30 mg/ml or 10–40 mg/ml, typically 20–30 mg/ml of galanthamine. Typical dosage rates when administering galanthamine by injection are in the range 5–1,000 mg per day depending upon the patient. For example, divided doses in the range 0.5–5 mg/kg body weight per day may prove useful. Typically, one might administer a dosage of 50–300 mg per day to a patient of a body weight of 40–100 kg, although in appropriate cases such dosages may prove useful for patients having a body weight outside this range. In other cases, dosages as low as 10 mg and as high as 500 mg may be appropriate for persons in this body weight range.

Galanthamine or its pharmaceutically-acceptable acid addition salts may also be administered orally, for example, as an aqueous suspension or a solution in aqueous ethanol or as a solid such as a tablet or capsule. Suspensions or solutions for oral administration are typically of about the same concentration as those used for injections. However, it may be desirable when administering the drug orally to use a higher dosage rate than when administering it by injection. For example, dosages up to 2000 mg per day may be used, such as dosages in the range 100–600 mg per day. In preparing such tablets or capsules, standard tablet or capsulemaking techniques may be employed. The dosage rate of galanthamine or its pharmaceutically-acceptable salt will normally be in the same range as for oral administration of a liquid. If desired, a pharmaceutically-acceptable carrier such as starch or lactose may be used in preparing galanthamine tablets. Capsules may be prepared using soft galatine as the encapsulating agent. If desired, such capsules may be in the form of sustained release capsules wherein the main capsule contains microcapsules of galanthamine which release the contents over a period of several hours thereby maintaining a constant level of galanthamine in the patient's blood stream.

The following test provides a good animal model for Alzheimer's disease in humans: A selective lesion is placed in a subcortical nucleus (nucleus basalis of Meynert) with a resultant cortical cholinergic deficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease. Numerous behavioral deficits, including the inability to learn and retain new information, characterizes this lesion. Drugs that can normalize these abnormalities would have a reasonable expectation of efficacyin Alzheimer's disease. Haroutunian, V, Kanof P, Davis, KL: Pharmacological alleviations of cholinergic-lesion-induced memory defects in rats. Life Sciences 37:945–952, 1985.

The following specific formulations may find use in treatment of Alzheimer's disease:

Tablets or capsules containing 5, 10 and 25 mg galanthamine hydrobromide to be taken four times a day, or a sustained-release preparation delivering an equivalent daily dose.

Parenteral solution containing 5 mg/ml.

Liquid formulation for oral administration available in 5 mg/5 ml and 25 mg/5 ml concentration.

There have been reports that galanthamine can cause cardiac arrythmias. In such cases, it may be desirable to

administer galanthamine in conjunction with another drug such as propanthelinbromide to control such arrythmias.

I claim:

1. A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

2. A method according to claim 1, wherein the administration is parenteral at a daily dosage of 5–1,000 mg of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

3. A method according to claim 2, wherein said dosage rate is 50–300 mg per day.

4. A method according to claim 1, wherein said administration is oral and is in the range 10–2000 mg per day.

5. A method according to claim 4, wherein said dosage rate of 100–600 mg per day.

6. A method according to claim 1, wherein galanthamine is administered at a dosage rate of 0.1 to 4 mg/kg body weight of a patient, parenterally.

7. A method according to claim 1, wherein galanthamine is administered intracerebroventricularly via an implanted reservoir at a dosage rate of 0.01 to 5.0 mg/kg day.

* * * * *

EXHIBIT B

Vol. 71, No. 1 Regd. No. 9, M. 429 JANUARY, 1974

The Antiseptic

A Monthly Journal of Medicine & Surgery

For the use of Registered Medical Practitioners only

Editorial & Publishing Office: 323-24, Thambu Chetty St., Madras-600001

Founded by the late Dr. U. RAMA RAU in 1904 Past Editor late Dr. U. KRISHNA RAU

Editor: U. VASUDEVA RAU, M.B., B.S.

'Grams: "ANTISEPTIC" P. O. Box 144 Phone: 22796

Subscription Rs. 15-00 Foreign Rs. 17-50 a year Single Copy Rs. 2-50 in advance

MEDICAL MANAGEMENT OF DEMENTIA*

P. A. BHASKER, M.D., D.M. (Neuro.),
Asst. Prof. of Neurology, Institute of Neurology, Government General Hospital, Madras-3

DEMENTIA is neither a disease *per se* nor a single symptom. It may be considered to be a clinical manifestation resulting from complex structural or functional changes in the most sophisticated mechanisms of the brain. The corrective treatment is usually therefore, one associated with a gloomy outlook, because a dementing process in most cases is a relentlessly progressive one, and very often not amenable even to diagnosis.

On the other hand, this gloomy picture is thoroughly wiped out and a favourable result readily obtained when one of the treatable underlying causes is detected; the prognosis becomes 'excellent' when the correctable cause is diagnosed early and found to be a metabolic or endocrine deficit (as in Pellagra, B_{12} deficiency or Myxœdema). In such cases, the dementia can be cleared up and the patient can have a complete "cure".

On the other hand, the dementing process can be arrested or reversed to a minor extent in some instances, where only a guarded prognosis can be offered. These situations include the cases of tumours (when removable), infections (like GPI) when they can be "successfully" arrested, post-traumatic dementias, and low pressure hydrocephalus.

The irreversible cases belong to the category of dementias where there is a progressive fall-out of neurons and the course of the illness is rapidly downhill. Therefore, the importance of a thorough diagnosis even at the first instance must be realised, because the compartmentalisation into treatable and untreatable dementias has to be made with the utmost care. Moreover it must be emphasised that in certain situations (like Myxœdema) a *late* diagnosis of the underlying cause may lead to irreversibility of the mental status, especially so, in the young developing brains.

With regard to progressive dementia, there appears very little to offer. Only management and no treatment is possible. The problem of who is going to manage the dementing individual arises next. Contrary to the older beliefs that the demented person (who is likely to be insane) has to be necessarily managed by a psychiatrist or an internist, it now appears that the Neurologist is the best person to handle them, and a neuropsychiatrist is the ideal person. The neurologist remains today at the centre of a triangle formed by the psychiatrist, the general physician and the neurosurgeon[1].

*Summarised from the talk given at the Institute of Neurology.
Specially contributed to the 'Annasaurus'.

The control of convulsions and involuntary movements are separate subjects by themselves. But what must be stressed is the importance of controlling these associated disorders which may sometimes assume greater importance than the dementia itself. For example, in cases of Huntington's chorea where the dementia may be very slowly progressive, the involuntary movements may present the main problem, when adequate control of the choreic movements enables the individual to go back to his work. Rewarding experiences are on record of having treated patients with Huntington's Chorea by giving Haloperidol, a very useful drug in the control of hyperkinetic dyskinesias.

The behavioural problems met with in patients with dementia are profound and so depending upon the nature of the behavioural disturbance, judicious use may be made of drugs, along with psychiatric care. General surgical therapy does not find a significant role in dealing with patients suffering from progressive dementia except when there is an isolated behavioural aberration that can be selectively tackled by Stereotaxy. Even then, any beneficial response is short-lived and soon overtaken by the dementing process.

A demented person obviously requires careful supervision and devoted nursing care as he will not be able by himself to attend to his own nutrition and personal cleanliness; he is also likely to be unmindful of any intercurrent illnesses that may supervene.

The restoration of higher cortical functions is difficult and was once considered to impossible; but it has lately gained importance. Luria and his colleagues have dealt with this problem in great detail. They have suggested measures of improving the higher functions in cases of local brain damage like tumour, head injury, infarct etc, by deinhibitory procedures and re-education of the rest of the brain. Deinhibition refers to the facilitation of acetylcholine activity by giving small daily doses of Cholinesterase inhibitors (Neostigmine, Gallanthamine etc.). Empirical measures, like trying anabolic steroids, vasodilators, nucleic acid preparations, amines and aminoacids are in vogue, but have not been of any great value. The problem of sending a demented individual back to his profession has to be adequately studied by the attending physician before coming to a definite decision. If he happens to hold a position requiring the use of proper judgement, it is better that he is relieved of such a responsible post and assigned a less exacting, general type of work.

The social aspects include adequate counselling in marriage affairs when a demented person or a relative of a demented

person seeks advice. The stigma associated with dementia is equal to that with epilepsy. This fact must be kept in mind by the physician, when confronted with a case of dementia and especially the relatives.

The problem of managing a demented individual in a very real one needing adequate judgement, judicious use of drugs, sympathetic nursing and proper counselling.

REFERENCES:

1. Zulch, K.J. (1969)—The Place of Neurology in Medicine and its Future in Vol. I (Disturbances of Nervous Function) of Handbook of Clinical Neurology, Ed.: Vinken, P. J. and Bruyn, G. W. North Holland Publishing Company—Amsterdam.

DEATHS INVOLVING PROPOXYPHENE

A STUDY OF 41 CASES OVER A TWO-YEAR PERIOD

Forty-one deaths occurred involving propoxyphene hydrochloride (Darvon) during a two year period. Ten patients died from propoxyphene intoxication alone, while 12 were victims of a propoxyphene alcohol combination, the latter number being identical to the deaths from a combination of barbiturates with alcohol seen during the same period. Five young women died from an ingestion of propoxyphene following an argument. Four patients could be categorized as drug abusers due to historical circumstances. The high levels of propoxyphene suggested habituation in three instances. Physicians should be alerted to the potential deleterious effects of indiscriminate use and abuse of propoxyphene, and should warn their patients not to drink alcoholic beverages when taking propoxyphene. They should use extreme caution when prescribing it to those in the younger age-group.

An impressive factor in this series is the availability of the drug to young people who, after a sudden argument, seem to find ingestion of pills a convenient gesture at attempted self-destruction. There were five cases of teenagers (all girls) in this series (aged 15 to 20 years) whose deaths were caused by propoxyphene intoxication, and in none of these were alcohol, other drugs or narcotics addiction involved. In two instances, the victims were found to be pregnant. Ten of the 22 patients who died from ingestion of propoxyphene alone, or propoxyphene in combination with alcohol, were over 40 years of age. while two of the deaths due to the combination were in patients over 60 years of age.

Concerning the manner of death, 17 of the 41 cases were classified as suicide, with six of these solely from the ingestion of propoxyphene.

Eighteen of the 41 patients received a prescription of propoxyphene from one or more private physicians. Seven of these patients eventually died from ingestion of propoxyphene or propoxyphene with alcohol. In 12 instances, the patient secured a prescription as an outpatient from a clinic. —(Sturner Q. William and Garriott C. James, *J.A.M.A.*, 5-3-1973).

EXHIBIT C

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JANSSEN PHARMACEUTICA N.V., JANSSEN, L.P., and SYNAPTECH, INC.,	)	
Plaintiffs,	)	
v.	)	Civil Action No. 05-356-KAJ (Consolidated)
ALPHAPHARM PTY., LTD.	)	
Defendant.	)	

DEFENDANT ALPHAPHARM PTY., LTD'S FIRST SUPPLEMENTAL RESPONSE TO INTERROGATORY NO. 2 OF PLAINTIFFS' FIRST SET OF INTERROGATORIES

Defendant Alphapharm Pty., Ltd ("Alphapharm" or "Defendant") submits the following supplemental response to Interrogatory No. 2 of Plaintiffs Janssen Pharmaceutica N.V., Janssen, L.P., and Synaptch, Inc.'s (collectively "Janssen" or "Plaintiffs") First Set of Interrogatories.

In submitting this supplemental response, Defendant does not waive any rights or objections which may otherwise be available, nor concede the relevance, competence, materiality, lack of privilege, or admissibility in evidence of such response.

All responses herein are submitted as presently advised, and without prejudice to Defendant's rights to modify, amend, revise, correct, supplement, add to or clarify such responses as any additional information may become known to Defendant.

GENERAL RESPONSES AND OBJECTIONS

The General Responses and Objections set forth in Defendant's Objections and Responses to Plaintiffs' First Set of Interrogatories are incorporated herein by reference and are applicable to each and every Interrogatory.

Stipulation Not to Contest Infringement. (*See* 12/22/2005 Stipulation, ¶ 4.) Defendant also objects to this Interrogatory to the extent this contention interrogatory is premature and may call for expert testimony. *See, e.g.*, Fed. R. Civ. P. 26(a)(2)(C). Defendant also objects to this Interrogatory as improperly being characterized as one interrogatory because its multiple subparts constitute separate interrogatories toward the presumptive 25 interrogatory limit. *See* Fed. R. Civ. P. 33(a). Defendant notes that the Court has not yet construed any claim terms, phrases, or clauses of the asserted claims nor have Plaintiffs provided Defendant with Plaintiffs' contentions as to the proper construction of any disputed claim terms, phrases, or clauses. Claim construction, which is an issue for the Court, is the first step in an infringement and/or invalidity analysis. Defendant reserves the right to supplement this response on this basis and on the basis of any additional discovery consistent with the Federal Rules of Civil Procedure, the Local Rules of Civil Practice and Procedure of the United States District Court for the District of Delaware, and any relevant Orders of the Court. Defendant further reserves the right to supplement its response to the extent that Plaintiffs change or otherwise supplement their contentions.

Subject to all of its objections, Defendant supplements its response to this Interrogatory as follows: Claim 1 of the '318 patent is directed to a "method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof." ('318 patent, claim 1). Claim 1 is invalid under 35 U.S.C. § 102(b) as anticipated by at least P.A. Bhasker, *Medical Management of Dementia*, THE ANTISEPTIC, 71(1): 45-47 (1974) ("the Bhasker Article"). The Bhasker Article teaches treating "irreversible," "progressive dementia," characterized by "a progressive fall-out of neurons and the course of the illness is

rapidly downhill," with "small daily doses" of "Gallanthamine." One of ordinary skill in the art at the time of the invention would have understood the type of dementia described in the Bhasker Article to be or include at least Alzheimer's disease and/or related dementias. *See, e.g.*, K.L. Rathmann *et al.*, *Alzheimer's Disease: Clinical Features, Pathogenesis, and Treatment*, DRUG INTELL. CLIN. PHARM., 18: 684-91 (1984) ("the Rathmann Article") (teaches at least that Alzheimer's disease is a type of dementia); MERCK MANUAL (14TH ed. 1982) (SYN RAZ 0006579-0006582) (teaches at least that Alzheimer's disease is a type of dementia "with a large loss of cells from the cerebral cortex and other brain areas," and that Alzheimer's dementia "progresses steadily."). One of ordinary skill in the art at the time of the invention would also have understood the Bhasker Article's "small daily doses" to be or include a "therapeutically effective amount." To the extent Plaintiffs' contend any limitation of claim 1 of the '318 patent is not satisfied (and Plaintiffs have not to date), the claimed subject matter would have been obvious to one of ordinary skill in the art at the time of the invention in light of the Bhasker article alone, or in light of prior art articles or knowledge in the field as described further below.

Claim 4 of the '318 patent includes all of the limitations of claim 1 and further includes the limitations of "oral administration" in the range of "10–2000 mg per day." ('318 patent, claim 4.) Dosages within this range are a matter of routine experimentation and oral administration of galanthamine.[1] For example, claim 4 of the '318 patent is invalid as obvious, under 35 U.S.C. § 103 in view of the combination of the Bhasker Article and at least one of: D. Daskalov *et al.*, *Nivalin: Application and Rehabilitation Treatment of Cerebral Diseases with Aphasic Syndromes*, MBI MEDICO-BIOLOGIC INFORMATION, 3: 9-11 (1980) ("the Daskalov

[1] The terms galantamine and galanthamine are used interchangeably in the art.

EXHIBIT D

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: '318 PATENT LITIGATION	:	Civil Action No. 05-356 (KAJ) (Consolidated)

DEFENDANTS BARR PHARMACEUTICALS, INC.'S AND BARR LABORATORIES INC.'S SUPPLEMENTAL OBJECTIONS AND RESPONSE TO PLAINTIFFS' INTERROGATORY NO. 2

Pursuant to Rules 26 and 33 of the Federal Rules of Civil Procedure, Defendants Barr Pharmaceuticals, Inc. and Barr Laboratories, Inc. (collectively "Barr") supplement their response to Plaintiffs' Interrogatory No. 2. Barr reserves the right to supplement or amend its objections and response as it obtains additional information during the course of discovery.

GENERAL OBJECTIONS

The following general objections to Plaintiffs' Interrogatories (including Definitions and Instructions) are hereby incorporated into Barr's supplemental objections and response to Plaintiffs' Interrogatory No. 2 as if fully set forth therein.

1. Barr objects to Plaintiffs' Interrogatories to the extent they call for responses that would require disclosure of information that is protected by the attorney-client privilege, the attorney work-product doctrine, or any other evidentiary privilege.

2. Barr objects to Plaintiffs' Interrogatories (including Definitions and Instructions) to the extent that they purport to impose discovery obligations beyond those required under the Federal Rules of Civil Procedure, the Local Rules of Civil Practice and Procedure of the United States District Court for the District of Delaware, and any applicable Orders of the Court or agreements between counsel. Barr will follow the governing rules, orders, and agreements in

RESPONSE:

Barr objects to this Interrogatory to the extent it seeks information relating to any claims other than claims 1 and 4 of the '318 patent, in light of the December 2, 2005 Stipulation Not to Contest Infringement. (*See* 12/2/2005 Stipulation, ¶ 4.) Barr objects to this Interrogatory to the extent this contention interrogatory is premature and may call for expert testimony. *See, e.g.*, Fed. R. Civ. P. 26(a)(2)(C). Barr objects to this Interrogatory as improperly being characterized as one interrogatory because its multiple subparts constitute separate interrogatories toward the presumptive 25 interrogatory limit. *See* Fed. R. Civ. P. 33(a). Barr notes that the Court has not yet construed any claim terms, phrases, or clauses of the asserted claims nor have Plaintiffs provided Barr with Plaintiffs' contentions as to the proper construction of any disputed claim terms, phrases, or clauses. Claim construction, which is an issue for the Court, is the first step in an infringement and/or invalidity analysis. Barr reserves the right to supplement this response on this basis and on the basis of any additional discovery consistent with the Federal Rules of Civil Procedure, the Local Rules of Civil Practice and Procedure of the United States District Court for the District of Delaware, and any relevant Orders of the Court. Barr further reserves the right to supplement its response to the extent that Plaintiffs change or otherwise supplement their contentions.

Subject to its general and specific objections, Barr responds to this Interrogatory as follows: Claim 1 of the '318 patent is directed to a "method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof." ('318 patent, claim 1.) Claim 1 is invalid under 35 U.S.C. § 102(b) as anticipated by at least P.A. Bhasker, *Medical Management of Dementia*, THE ANTISEPTIC, 71(1): 45-47 (1974) ("the Bhasker Article"). The Bhasker Article teaches treating "irreversible," "progressive

dementia," characterized by "a progressive fall-out of neurons and the course of the illness is rapidly downhill," with "small daily doses" of "Gallanthamine." One of ordinary skill in the art at the time of the invention would have understood the type of dementia described in the Bhasker Article to be or include at least Alzheimer's disease and/or related dementias. *See, e.g.*, K.L. Rathmann *et al.*, *Alzheimer's Disease· Clinical Features, Pathogenesis, and Treatment*, DRUG INTELL. CLIN. PHARM., 18: 684-91 (1984) ("the Rathmann Article") (teaches at least that Alzheimer's disease is a type of dementia); MERCK MANUAL (14th ed. 1982) (SYN RAZ 0006579-0006582) (teaches at least that Alzheimer's disease is a type of dementia "with a large loss of cells from the cerebral cortex and other brain areas," and that Alzheimer's dementia "progresses steadily."). One of ordinary skill in the art at the time of the invention would also have understood the Bhasker Article's "small daily doses" to be or include a "therapeutically effective amount." To the extent Plaintiffs contend any limitation of claim 1 of the '318 patent is not satisfied (and Plaintiffs have not to date), the claimed subject matter would have been obvious to one of ordinary skill in the art at the time of the invention in light of the Bhasker article alone, or in light of prior art articles or knowledge in the field as described further below.

Claim 4 of the '318 patent includes all of the limitations of claim 1 and further includes the limitations of "oral administration" in the range of "10–2000 mg per day." ('318 patent, claim 4.) Dosages within this range are a matter of routine experimentation and oral administration of galantamine[1] was well known. For example, claim 4 of the '318 patent is invalid as obvious, under 35 U.S.C. § 103 in view of the combination of the Bhasker Article and at least one of: D. Daskalov *et al.*, *Nivalin. Application and Rehabilitation Treatment of Cerebral Diseases with Aphasic Syndromes*, MBI MEDICO-BIOLOGIC INFORMATION, 3: 9-11

EXHIBIT E

REDACTED

CERTIFICATE OF SERVICE

I hereby certify that on the 28th day of November, 2006, the attached **REDACTED PUBLIC VERSION OF PLAINTIFFS' MEMORANDUM IN SUPPORT OF MOTION FOR PARTIAL SUMMARY JUDGMENT REGARDING ANTICIPATION UNDER 35 U.S.C. § 102** was served upon the below-named counsel of record at the address and in the manner indicated:

John C. Phillips, Jr., Esquire — HAND DELIVERY
Phillips, Goldman & Spence, P.A.
1200 North Broom Street
Wilmington, DE 19806

Lynn M. Ulrich, Esquire — VIA FEDERAL EXPRESS
Winston & Strawn LLP
35 West Wacker Drive
Chicago, IL 60601

Frederick L. Cottrell, III, Esquire — HAND DELIVERY
Richards, Layton & Finger
One Rodney Square
Wilmington, DE 19801

Alan H. Bernstein, Esquire — VIA FEDERAL EXPRESS
Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd.
1635 Market Street, 12th Floor
Philadelphia, PA 19103

/s/ Tiffany Geyer Lydon

Tiffany Geyer Lydon